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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	**PAPER NUMBER**
1633	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/626,159	SHARMA, VINOD	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3 and 46-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 3, 46-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/7/07 has been entered.

Amended claims 1, 3, 46-56 and new claim 57 are pending in the present application, and they are examined on the merits herein.

Claim Objections

Claim 3 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 51. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Amended claims 1, 46-48 and 57 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1117. The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." Vas-Cath Inc. v. Mahurkar, 19USPQ2d at 1116.

Applicant's invention is drawn to an implantable bio-ablation composition comprising **a first polynucleotide encoding any dominant negative N-terminal truncated α1 subunit of an L-type Ca^{2+} channel** and a second polynucleotide encoding a Giα subunit.

However, apart from the specific disclosure that the expression of L-type Ca channel can be suppressed through the use of **the dominant negative Ca(v)1.2 with an ascidian 3-domain type alpha 1 subunit** (paragraphs 0037 and 0072), the instant specification fails to describe **sufficient relevant characteristics of a representative number of other species** for **a broad genus** of a first polynucleotide encoding a

dominant negative N-terminal truncated α1 subunit of an L-type Ca^{2+} channel in the bio-ablation composition as claimed. **There is no simple direct structural/functional relationship between an N-terminal truncation of any α1 subunit of an L-type Ca^{2+} channel or of the ascidian 3-domain type with its dominant negative activity apart from the already described dominant negative Ca(v)1.2 with an ascidian 3-domain type alpha 1 subunit** as evidenced at least by the teachings of Ebihara et al. (FEBS Letters 529:203-207; 2002). Ebihara et al already stated "In our case, t**he 3-domain-mutant of $Ca_v2.1$ and $Ca_v3.1$ did not show a significant inhibitory effect on wild-type channels. Therefore, the mechanism of 3-domain-mutant of $Ca_v1.2$ should be different from the other Ca_v dominant negative effects**" (page 206, col. 2, middle of second paragraph). Accordingly, what are the essential structural characteristics possessed by numerous other encoded dominant negative N-terminal truncated α1 subunits of an L-type Ca^{2+} channel as claimed broadly in the implantable bio-ablation composition of the present invention?

The claimed invention as a whole is not adequately described. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure for a representative number of species for a broad genus of a first polynucleotide encoding any dominant negative N-terminal truncated α1 subunit of an L-type Ca^{2+} channel in the bio-ablation composition

as claimed, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991). One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 49-50 and 56 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. ***This is a new ground of rejection necessitated by Applicant's amendment.***

Claims 49-50 and 56 are dependent on cancelled claims 6 and 2. Accordingly, it is unclear what exactly do Applicants intend to claim. The metes and bounds of the claims are not clearly determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Amended claims 1, 3, 46-48 and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donahue et al. (US 2002/0155101; IDS) in view of Murata et al. (Circulation 106:19, abstract 36, 2002; IDS) for the same reasons already set forth in the Office action mailed on 6/7/07 (pages 8-10). ***The same rejection is restated below.***

Donahue et al. disclosed a composition comprising one or a combination of polynucleotides that encode the inhibitory Gαi2 subunit, G-protein subunit, connexin, gap junction protein and at least one ion channel protein including L-type Ca channel subunits having dominant negative activity, and others including genes for proteins that affect the expression, processing or function processing of the proteins affecting arrhythmias to cause a decrease in speed of conduction through at least the atrioventicular (AV) node (see at least the abstract; paragraphs 36-39, 44-53, 98 and 108). Donahue et al further teaches that a dominant negative protein has capacity to inactivate an endogenous protein (paragraphs 63-65), and that nucleic acid delivery systems including adeno-associated viral vector can be used (paragraph 71). Donahue et al disclosed by exemplification showing that over-expression of Gαi2 subunit is capable of decreasing speed of conductance through the atrioventricular node in an

animal system as determined by standard electrophysiological assay (paragraphs 0101-0104, and examples).

Donahue et al does not teach specifically a composition further comprising a coding sequence coding for a molecule that decreases expression of L-type Ca channels, specifically a sequence encoding kir/GEM; even though the reference teaches a composition to include polynucleotides encoding at least one ion channel protein including L-type calcium channel subunits having dominant negative activity, and others including genes for proteins that affect the expression, processing or function processing of the proteins affecting arrythmia.

At the effective filing date of the present application, Murata et al already disclosed a vector encoding kir/GEM and that exogenous expression of kir/GEM reduced L-type calcium current that mimics pharmacological calcium channel blockade in adult guinea pigs (see the abstract). Murata et al further disclosed that kir/GEM was previously demonstrated reduce calcium current by inhibiting alpha subunit trafficking of L-type calcium channels in PC12 cells (decreasing expression of L-type calcium channels).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Donahue et al. by also incorporating a vector encoding kir/GEM in their composition to modulate the electrical property of the heart in an experimental model, particularly for decreasing the speed of conduction through at least the atrioventicular (AV) node in a mammal, in light of the teachings of Murata et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Murata et al already disclosed that exogenous expression of kir/GEM reduced L-type calcium current that mimics pharmacological calcium channel blockade in adult guinea pigs, and this is another approach that is resulting in inactivating the activity of endogenous L-type calcium channels.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Donahue et al., and Murata et al.; coupled with the high level of skill of an ordinary skilled artisan in the relevant art. The modified composition resulting from the combined teachings of Donahue et al. and Murata et al. is indistinguishable from the bio-ablation composition of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Argument

Applicant's arguments related in part to the above rejection in the Amendment filed on 8/7/07 (pages 7-8) have been fully considered, but they are respectfully not found to be persuasive.

Applicant argues basically that although the Donahue et al reference teaches that decreases in conduction of at least about 10%, preferably about 20 to 50% or more are useful, such a decrease for treating arrhythmia does not amount to effectively extinguishing conduction with the bio-ablation composition of the present application that would not be useful for treating arrhythmias. Additionally, there is nothing in the

combined teachings of Donahue et al and Murata et al that would lead one to formulae a composition that would effectively extinguish conduction through the AV node.

Firstly, please note that the Donahue et al reference states specifically "Decrease of at least about 10% relative to baseline in the assay, preferably about 20% to 50% **or more**, are useful for many invention embodiments" (last sentence of paragraph 39). This statement clearly implies that Donahue et al also contemplate a 100% decrease relative to the baseline.

Secondly, **please note with respect to a composition claim its intended use is not given any patentable weight in light of the prior art**. For this instance, regardless whether the composition that is taught by Donahue et al is intended for arrhythmia treatment, the modified composition resulting from the combined teachings of Donahue et al. and Murata et al. has the same essential components and is indistinguishable from the bio-ablation composition of the present application.

Thirdly, Please, also note that where, as here, the claimed and prior art products are identical **or** substantially identical, or are produced by identical **or** substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke. Whether the rejection is based on "inherency" under 35 USC 102, or "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195

USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972).

Accordingly, amended claims 1, 3, 46-48 and 51-55 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donahue et al. in view of Murata et al. for the same reasons already set forth in the Office action mailed on 6/7/07 (pages 8-10).

Amended claims 1, 46-48 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Donahue et al. (US 2002/0155101; IDS) in view of Ebihara et al. (FEBS Letters 529:203-207, 2002). ***This is a new ground of rejection necessitated by Applicant's amendment.***

Donahue et al. disclosed a composition comprising one or a combination of polynucleotides that encode the inhibitory Gαi2 subunit, G-protein subunit, connexin, gap junction protein and at least one ion channel protein including L-type Ca channel subunits having dominant negative activity, and others including genes for proteins that affect the expression, processing or function processing of the proteins affecting arrhythmias to cause a decrease in speed of conduction through at least the atrioventicular (AV) node (see at least the abstract; paragraphs 36-39, 44-53, 98 and 108). Donahue et al further teaches that a dominant negative protein has capacity to inactivate an endogenous protein (paragraphs 63-65), and that nucleic acid delivery systems including adeno-associated viral vector can be used (paragraph 71). Donahue et al disclosed by exemplification showing that over-expression of Gαi2 subunit is capable of decreasing speed of conductance through the atrioventricular node in an

animal system as determined by standard electrophysiological assay (paragraphs 0101-0104, and examples).

Donahue et al does not teach specifically a composition further comprising a coding sequence coding for dominant negative N-terminal truncated α1 subunit of an L-type Ca^{2+} channel or of the ascidian 3-domain type ; even though the reference teaches a composition to include polynucleotides encoding at least one ion channel protein including L-type calcium channel subunits having dominant negative activity, and others including genes for proteins that affect the expression, processing or function processing of the proteins affecting arrythmia.

At the effective filing date of the present application, Ebihara et al already taught that recombinant expression of the dominant negative 3-domain-type Cav1.2 α1 subunit lacking an N-terminus and the first domain specifically suppresses L-type calcium channel activity *in vivo* (see at least the abstract).

It would have been obvious for an ordinary skilled artisan to modify the teachings of Donahue et al. by also incorporating a vector encoding a Cav1.2 protein lacking an N-terminus and the first domain that specifically suppresses L-type calcium channel activity in their composition to modulate the electrical property of the heart in an experimental model, particularly for decreasing the speed of conduction through at least the atrioventicular (AV) node (e.g., at least about 10% relatively to the baseline, preferably about 20% to about 50% or more) in a mammal, in light of the teachings of Ebihara et al.

An ordinary skilled artisan would have been motivated to carry out the above modification because Ebihara et al already demonstrated successfully that recombinant expression of the dominant negative 3-domain-type Cav1.2 α1 subunit lacking an N-terminus and the first domain specifically suppresses L-type calcium channel activity *in vivo*; and Donahue et al also taught specifically that the disclosed composition may include polynucleotides encoding at least one ion channel protein including L-type calcium channel subunits having dominant negative activity.

An ordinary skilled artisan would have a reasonable expectation of success in light of the teachings of Donahue et al., and Ebihara et al.; coupled with the high level of skill of an ordinary skilled artisan in the relevant art. The modified composition resulting from the combined teachings of Donahue et al. and Ebihara et al. is indistinguishable from the bio-ablation composition of the present application.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's SPE, Joseph T. Woitach, Ph.D., may be reached at (571) 272-0739.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1633; Central Fax No. (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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QUANG NGUYEN, PH.D.
PRIMARY EXAMINER